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A cascade enyne/ring closing metathesis approach to angularly fused dioxatriquinanes†

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An expedient and first tandem enyne/ring closing metathesis approach on a sugar furanose template leading to a novel angularly fused dioxa-triquinane is described here.

Polyquinane natural products, especially angularly fused and linearly fused triquinanes have generated a great deal of interest among synthetic chemists in the last two decades primarily because of their aesthetically pleasing architecture and interesting biological properties.[1] As a consequence, several approaches and strategies,[2] especially cascade radical methods,[3] have been employed to meet the challenges posed by this family of compounds. Despite the wealth of literature available for the isolation of carbocyclic triquinanes, there are not many reports on the isolation[4] or syntheses[5] of its structurally novel and biologically potent siblings oxa- and dioxatriquinanes (Fig. 1). Interestingly, some of the reported syntheses of carbocyclic triquinanes proceed *via* oxatriquinanes and a few of these oxatriquinanes exhibited potent *in vitro* cytotoxic activity against murine leukemia cells and KB human epidermoid carcinoma cells.[6]

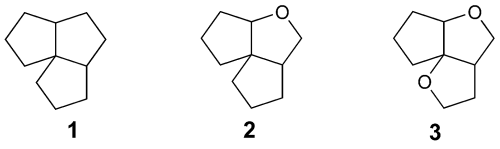
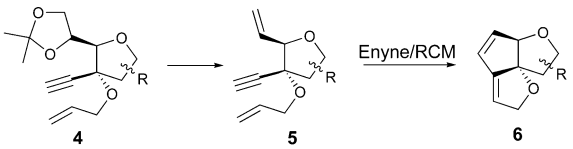


Fig. 1 Triquinane, oxa- and dioxatriquinanes.

Sugar templates have been wonderful starting materials for the syntheses of several natural and non-natural products. They have been elegantly transformed[7] into triquinanes, oxatriquinanes and dioxatriquinanes involving a cascade radical cyclization. However, to the best of our knowledge, a tandem metathesis[8] strategy has not been looked at successfully for synthesizing triquinanes thus far. As a part of our chiron approach program[9] directed toward the synthesis of biologically active compounds, and also in view of the potential utility of oxatriquinanes, we developed interest in the synthesis of angularly fused oxatriquinanes based on metathetic reactions.[10] Herein, we report our initial successful results in the synthesis of a sugar-based dioxatriquinane by a tandem enyne/ring closing metathesis reaction. From a synthetic perspective, we envisaged that the enyne **4** could be easily made from a sugar template and in a couple of steps it could be transformed into the dienyne **5**, a precursor for the key tandem enyne/ring closing metathesis reaction leading to the required dioxatriquinane **6** as shown in Scheme 1.



Scheme 1

† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H and ^{13}C NMR spectral data for new compounds. See http://www.rsc.org/suppdata/cc/b4/b409665g/

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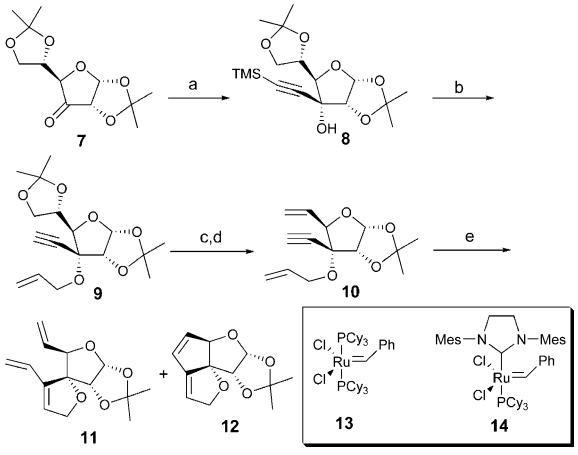
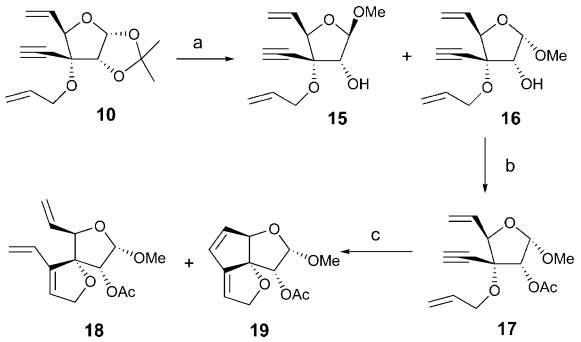
Our route to the synthesis of dioxatriquinane commenced from the readily available ketone **7**. Exposure of the ketone **7**, to lithium trimethylsilylaetylide, generated *in situ* from trimethylsilylacetylene and ^{n}BuLi, afforded the alcohol **8** in high yield. The stereochemical outcome of addition of organomagnesium and organolithium reaction to the ketone is well established[11] and the reagent is expected to come from the top face leading to the alcohol **8** as shown in Scheme 2. Reaction with NaH and allyl bromide achieved protection of the tertiary alcohol **8** with concurrent removal of the trimethylsilyl group to generate the enyne **9**. Then we sought to install the other alkene moiety required for the tandem reaction. This was successfully achieved by first selectively deprotecting the more exposed acetonide group under mild acidic conditions followed by converting the resulting vicinal diol into the desired dienyne **10** in a single step following Garregg's protocol.[12] This set the stage for our proposed cascade enyne metathesis/ring closing metathesis reaction. However, all our attempts to successfully carry out the cascade enyne/RCM of dienyne **10** with Grubbs' first generation (**13**) and second generations catalysts (**14**) resulted in the fomation of simple enyne metathesis product **11** as the only isolable product in good yield. We attempted this reaction under a variety of conditions with very little effect on the final outcome.

At this point, we decided to remove the acetonide group of **10**, anticipating a relief in the ring strain, which in turn could probably bring the two double bonds closer after the initial enyne metathesis. Thus, the acetonide group was removed under standard conditions in the presence of methanol to provide a readily separable anomeric mixture of hydroxy dienynes **15** and **16** in the ratio 1:2.7 with a global yield of 89% (Scheme 3). The major isomer **16** was protected as acetate (**17**) before subjecting to the tandem enyne/ring closing metathesis conditions. Then, we examined different conditions for the key tandem metathesis reaction and the results are summarised in Table 1. Our initial attempt to use 10 mol% of Grubbs' first generation catalyst **13** under Argon atmosphere failed to promote



Scheme 2 *Reagents and conditions*: (a) TMSacetylene, *n*-BuLi, THF, 0 °C, RT, 80% (b) NaH, allylbromide, DMF, 2 h, 78% (c) 60% AcOH, RT, 18 h (d) PPh_3, I_2, Imidazole, toluene, reflux, 5 h, 85% for two steps (e) Grubbs' catalysts (**13/14**), CH_2Cl_2 (~3 mM), reflux, 12 h (65–78%).

even the normally facile enyne metathesis reaction. Though ethylene atmosphere has been known to promote enyne metathesis reaction, in our case, there was no significant improvement and we could obtain only traces of enyne metathesis product **18**. When the more reactive Grubbs' second generation catalyst **14** was employed under ethylene atmosphere, only traces of the required cascade metathesis product **19** were observed and regular enyne metathesis product **18** being the major product. This is quite understandable and can be easily rationalized as ethylene atmosphere could facilitate the ring opening of **19**. Gratifyingly, the dienyne **17** underwent a smooth tandem enyne metathesis/RCM, under Argon atmosphere, to afford a mixture of **18** and **19** in approximately 1:2 ratio with a combined yield of around 95%. From the Table 1, it is clear that solvents do not make much difference in the overall distribution of the products whereas catalyst and reaction atmosphere do make significant difference in the final ratio of the products.



Scheme 3 *Reagents and conditions*: (a) Conc. HCl, MeOH, RT, 36 h, 89% (3:11) (b) Ac_2O, Py, DMAP, RT, 8 h, 90% (c) Grubbs' catalyst, solvent, reflux, 12 h (see Table 1).

Table 1 Effect of catalysts and solvents on enyne/RCM

Sub.	Catalyst	Conditions	Product ratio [**18**:**19**]	
17	**13** (10 mol%)	CH_2Cl_2, reflux, 36 h (Argon)	No reaction	
17	**13** (10 mol%)	CH_2Cl_2, reflux, 36 h (Ethylene)	08	00
17	**14** (5 mol%)	CH_2Cl_2, reflux, 36 h (Ethylene)	61	13
17	**14** (5 mol%)	Toluene, 80 °C, 36 h (Ethylene)	73	05
17	**14** (5 mol%)	CH_2Cl_2, reflux, 36 h (Argon)	**36**	**60**
17	**14** (5 mol%)	Toluene, 80 °C, 36 h (Argon)	**35**	**59**

In summary, we have developed a simple and efficient enantiospecific route to angularly fused dioxatriquinanes involving a tandem enyne/ring closing metathesis reaction as the key step. We also observed and indirectly proved that the presence of an acetonide group in the system hindered the ring closing metathesis after the initial enyne metathesis reaction. We are extending this methodology to the synthesis of various carbocyclic angularly fused triquinanes in our laboratory.

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